REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-24 were pending. In this response, claims 7 and 16 are cancelled without prejudice, and claims 1-6 and 8-15 are amended for further clarity. No new matter is added. Further, climas 17-24 have been withdrawn as being directed to a non-elected invention group. Accordingly, claims 1-6, 8-15, and 17-24 are pending, and claims 1-6 and 8-15 are at issue.

Notice of Related Applications

The Examiner is informed of the existence of the following related applications:

US Application No. 10/394,085 filed March 21, 2003

US Application No. 10/394,086 filed March 21, 2003

US Application No. 11/429,558 filed May 5, 2006

Priority

The Examiner has indicated that the present claims are entitled to a priority date of October 2, 2001, the filing date of US 09/969,357 (the "'357 application").

Applicants respectfully request that the Examiner accord the present claims a priority date of October 2, 2000, the filing date of Danish priority application serial no. DK PA 2000 01456 (the "'01456 application"). Examples 1-3 of the '01456 application (which correspond to Example 1 of the '357 application) disclose culturing Factor VII-producing cells in 100-l cultures, which are large-scale cultures according to the present claims.

Information Disclosure Statement

The Examiner has indicated that the Information Disclosure Statement filed December 2, 2003 was defective. This objection is not understood. In addition to the references listed on page 2 of the Information Disclosure Statement, a Form PTO-1449 was also filed, listing the same references, and this form has been initialed by the Examiner. Applicants respectfully request clarification.

Formalities

The Examiner has objected to the Title, Abstract, and specification. In this response, the Title, Abstract, and specification have been amended accordingly. It is respectfully submitted that the objections have been rendered moot and may be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 2-16 have been rejected under 35 U.S.C. §112, second paragraph, for indefiniteness, for the recitation of: "macrocarrier culture" (claim 7); "maintaining step comprises sedimentation" (claim 10); "gradual or continuous" (claim 14); "cells having a second predetermined density" (claims 15 and 16); and allegedly improper antecedent usage (claims 2-14).

In this response, claims 7 and 16 have been cancelled; claim 14 has been amended to delete the phrase "or continuous"; claim 15 has been amended to clarify that the culture is maintained at a second predetermined density; and claims 2-6 and 8-15 have been amended to utilize the antecedent language suggested by the Examiner. It is believed that these amendments have overcome these grounds for rejection.

With respect to claim 10, Applicants respectfully traverse the rejection. The Examiner contends that "sedimentation would not support cell growth and is, therefore, not a 'maintaining step'" (Office Action at page 5).

Taken in the context of claim 9 (on which claim 10 has now been made dependent), the maintaining step may properly include a step of removing a portion of the culture, followed by sedimenting the carriers prior to harvesting.

Based on the current amendments and remarks, it is respectfully submitted that the present claims are definite and that these rejections may be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-16 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement and lack of written description, based on the recitation of "Factor VII-related polypeptides". The Examiner contends that the specification does not support the scope of the claims and that Applicants did not have possession of the full scope of the claims at the time of filing. This rejection is respectfully traversed.

The present invention is not directed towards Factor VII-related polypeptides themselves but rather to methods of producing Factor VII and related polypeptides in mammalian cells in the absence of serum or animal-derived components. Accordingly, it is believed that the present specification (which lists or references numerous examples of such polypeptides, see, e.g., page 7, line 23- page 8, line 4) more than adequately enables and describes application of the presently claimed production methods to Factor VII variants and derivatives.

To expedite prosecution, however, in this response the claims have been amended to delete references to Factor VII-related polypeptides. It is respectfully submitted that this rejection has been overcome.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 5, 6, 15, and 16 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ragni, *Haemophilia* 7(supp 1):28-35, 2000; in view of Schmidtchen et al., *Am.J.Hum.Genet.* 62:64, 1998. The Examiner contends that Ragni discloses methods for large-scale production of Factor VII in recombinant cells in serum-containing cultures; that Schmidtchen et al. disclose methods for protein production in recombinant CHO cells in the absence of serum; and that it would have been obvious to combine these teachings to achieve the presently claimed invention. This rejection is respectfully traversed.

First, Applicants point out that Ragni is not prior art against the present claims, as Danish priority application DK PA 2000 01456 discloses the subject matter of the present claims and predates Ragni (see above).

Second, Applicants do not dispute that serum-free culture of CHO cells (at least in small scale) was known, and that serum-free culture of Factor VII-expressing cells, per se, may have been "obvious-to-try". However, nothing in Ragni, with or without Schmidtchen et al. could have provided one of ordinary skill in the art with any expectation of success at producing bioactive Factor VII (i) under serum-free conditions *and* (ii) in large scale cultures suitable for industrial use.

Ragni, to the contrary, discusses numerous challenges that were still extant in 2001 that could prevent large-scale production of clotting factors in serum-free cultures, such as, e.g., stability (provided in part by serum proteins) and immunogenicity (an unpredictable property depending at least in part on culture conditions) (see, Ragni, page 31, second column). Ragni, in

fact, proposes to solve these problems by altering the sequence/structure of the clotting factors (see, e.g., page 32, first column- page 33, second column), not by optimizing production conditions as in the present invention.

Schmidtchen et al. does nothing to supplement the limited teachings of Ragni. Schmidtchen et al. merely demonstrates that 100-mm plates of recombinant CHO cells (expressing a different protein) could be subjected to serum-free conditions. There is no hint or suggestion in Schmidtchen et al. of any method for large-scale production in serum-free conditions.

The sensitivity of protein (particularly glycoprotein) structure and function to variations in culture conditions means that it is unpredictable if a particular protein can be produced in active form under serum-free conditions. The present inventors have further succeeded in producing Factor VII under serum-free conditions in large scale, which could not have been predicted based on anything in the cited references. Accordingly, it is respectfully submitted that the present claims are non-obvious over the cited references.

Claim 3 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Ragni and Schmidtchen et al. further in view of Weikert et al., *Nature Biotechnol.* 17:1116, 1999. The Examiner contends that Weikert et al. discloses a recombinant CHO cell overexpressing sialyltransferase and that it would have been obvious to use such cells to express Factor VII. Claims 4 and 9-14 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Ragni and Schmidtchen et al. further in view of Chen et al., *Curr.Protoc.Prot.Sci* 5.10, 1998. The Examiner contends that Chen et al. discloses steps that could be used in large-scale culture of mammalian cells and that it would have been obvious to combine the teachings of these references to achieve the presently claimed invention. Finally, Claim 8 has been rejected under 35 U.S.C. § 103(a) as unpatentable over Ragni and Schmidtchen et al. further in view of Reiter, Cytotechnol. 3:271, 1990. The Examiner contends that Reiter discloses the use of macroporous carriers and that it would have been obvious to apply their use to expression of Factor VII. These rejections are respectfully traversed.

As discussed above, results obtained for recombinant expression of one protein cannot be extrapolated to other proteins, especially with respect to glycosylation patterns. The present inventors have discovered that large-scale expression of Factor VII under serum-free conditions in CHO cells results in the elaboration of specific oligosaccharide structures and, overall, produces a polypeptide with better bioavailability than that observed in Factor VII produced under

serum-containing conditions in BHK cells. Furthermore, even knowing methods for possible scale up of mammalian cells (including the use of carriers), one of ordinary skill could not have had any reasonable expectation of achieving the present invention. Contrary to the Examiner's contention, nothing in Weikert et al., Chen et la., or Rieter can render the present invention obvious.

Based on the above amendments and remarks, it is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

Respectfully submitted,

Date: December 20, 2006

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